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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/069,883 | 05/01/2002 | Francois Mallet | 112062 | 3896 |

7590 05/05/2004

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Alexandria, VA 22320

| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/069,883 | MALLET ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *12-20, 22-25 and 27-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/14/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence letter*.

## DETAILED ACTION

Preliminary amendment A filed on march 02, 2002 has been acknowledged. Clams 21-24 and 26 have been canceled. Claims 3, 9-11, 15, 16, 18, 23-25, 27-31 and 34 have been amended. Claims 1-21, 25, 27-37 are pending.

### *Election/Restrictions*

1. Applicant's election with traverse of Group I, claims 1-11 in the scope of epithelial cells in Paper No. 14 is acknowledged. The traversal is on the ground(s) that HERV-W induced fusion all type of cells provides a special technical feature, such that all of species of claims 1-11 have unity of invention. Moreover, the searches of claims 1-11 will be related to the claims 12-20, 25 and 27-34. Therefore, it is respectfully submitted that the search and examination of entire application could be made without serious burden.

2. Applicants' argument has been fully considered. However, it is not found persuasive. Because the common technical feature of detecting the expression of human endogenous retroviral envelope protein of SEQ ID NO: 1 has been taught by Blond et al. Therefore, the claimed invention lack the common technical feature that link all claims together. Moreover, group I of claims 1-11 is directed to a method of detecting an expression of a human endogenous retrovirus polypeptide; whereas the claims 12-20, 25 and 27-34 are directed to a method of using a nucleic acid sequence as a gene therapy. They do not shear same common technical features and require different searches. Therefore, they are not rejoined.

3. Regarding to the species election, because Blond et al. also disclose that the expression of polypeptide of SEQ ID NO: 1 is detected in different kinds of tissue cells (See Fig. 1 on page 1177), they also lack the unity of invention.

4. MPEP recites: In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. Therefore, in the instant case, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability

5. The requirement of lack of unity is still deemed proper and is therefore made FINAL.

***Sequence requirements***

6. This application contains sequence disclosures on pages 28-29 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

7. Full compliance with the sequence rules by inserting a proper sequence identification number (SEQ ID NO) is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In the instant case, the claims are drawn to a method for detecting expression of a polypeptide. However, there is no particular assay recited in the claims, and the claims are written incompletely. It is well known in the art that detection of a polypeptide expression has to be carried out by some necessary assay. In generally, a western blot is used for detecting the protein or northern blot for mRNA or a southern blot or PCR for DNA. The examiner notices

that claims recite some structural and functional characteristics of the polypeptide; however, these recitations are limitations of claimed polypeptide, and are not any manipulating step of claimed method. These affect the depended claims 3-11.

11. Claims 1-2, 5, 7, 10, and 11 are vague and indefinite in that the recitation of "preferably" is a relative word, which fails to define clearly whether the claimed narrower range of preferred polypeptide is a limitation. Therefore, it is considered indefinite.

12. Claims 1-2 and 5 are further confusing for recitation that polypeptide comprises at least more than 5 or 20 amino acids. In addition, the metes and bounds of recited " a fragment of SEQ ID NO: 1" in line 9-1 of claim 1 are not defined. Because the recitations do not given any low and up limitations of claimed fragment, and one amino acid or two amino acid residues can be all considered as a fragment of SEQ ID NO: 1; the claims are considered as indefinite.

13. Moreover, claims 1-2, 5 and 7 describe that the polypeptide has at least 80 to 95 % identities to the SEQ ID NO: 1. Applicants are reminded that the identity, homology or sequence similarity can be calculated by a variety of different methods, whereby the calculated identity between two sequences will be quite different depending on the algorithm used for calculation. Applicant has referred the claimed polypeptide to various % identities, but there is no indication of the utilized algorithm to calculate the identity sequences. Furthermore, the calculation of "identity" is affected by variables such as the relative weight given to the sequence gaps versus mismatches, or whether conservative substitutions are weighted differently from non-conservative substitutions. Therefore, the claims are also considered indefinite.

14. Claim 1 also recites the limitation "the" in fusogenic power. There is insufficient antecedent basis for this limitation in the claim. Because the fusogenic is not inherent characteristic of all polypeptide or peptide, the recitation of "the" in fusogenic" really lacks the antecedent basis.

15. The claim 9 is also vague in that the use of a relative term of "derived". Since the specification does not provide a standard for ascertaining the requisite degree of derivation and the term of "derivation" has many interpretations, one of ordinary skill in the art would not reasonably encompass of the scope of the invention. Therefore the claim is considered as indefinite.

***Claim Rejections - 35 USC § 112***

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a cell-to-cell fusion by transfecting the TELac2 cells with the full-length envelope protein of human endogenous retrovirus W (HERV-W) envelope protein, does not reasonably provide enablement for producing a cell-cell fusion by using any fragment of SEQ ID NO: 1 transfected into in any or all type of cells from any kinds of tissue origins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

18. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

19. 1) & 2). State of art and Unpredictability. The state of art teaches that some envelope proteins of retroviruses are able to induce a fusion when it is expressed in cells. However, not every retrovirus encoded envelope protein is fusogenic. Some of them are not fusogenic. For example, certain strains of HIV isolates do not induce syncytium, which is called non-syncytium-inducing (NSI) phenotype HIV although they shear same receptor and co-receptor with other syncytium-inducing (SI) phenotype HIV as evidenced by Tebit et al. (AIDS RESEARCH AND HUMAN RETROVIRUSES 2002, Vol. 18 No.10, pp. 39-48, see Table 2 on page 42 and Fig. 3 on page 46). State of art also teaches that the fusogenic domain of retrovirus envelope protein is located at the transmembrane (TM) glycoprotein gp41.However, a mutation

in the principle immunodominant domain (PID) of gp41 can severely affect envelope protein mediated syncytium formation as evidenced by Pancino et al. (J. Virol. 1995, Vol. 69 (4), pp. 2110-2118, see abstract, Fig. 1 on page 2111, section of Effects of PID loop exchange on envelope fusogenic properties on page 2114 and Fig. 5 on page 2115). Therefore, it is very unpredictable that any fragment that comprises on any size as small as 5 amino acids or any series of 20 amino acids of SEQ ID NO: 1 is able to induce a syncytium formation. For example, a genome sequence of Chlamydia has a same amino acid sequence ALGTGIG to that of current claimed polypeptide from amino acid residues position 332-338; however, it does not has any fusogenic activity (Stephens et al. Science 1998, Vol. 282, pp. 754-759).

20. 3) & 4) Number of working examples and Amount of guidance. Applicants only teach that a cell-cell fusion can be observed between the TELCeB6 cells transfected with the full-length envelope protein of human endogenous retrovirus-W and certain animal cell lines including human Rhadbomyosacoma, epidermoid carcinma, epithelioid carcinoma, monkey fibroblastoma and pig endothelium. However, this kind of fusion cannot be observed in other animal cell lines, such as rat, mouse quail cells, indicating that the fusion could involve other cellular factors. Moreover, the specification does not teach any other fragment that is able to induce the cell-cell fusion. The specification is deficient for teaching or guidance regarding which part of the sequence of SEQ ID NO: 1 is important for the fusion and other amino acid residues may be negligible for the fusion and can be mutated.

21. 5) Scope of the claims. While the specification only teach one example of full-length envelope of HERV-W is able to induce a fusion in a imitated animal cell lines, the scope of the claimed method broadly read on a method for detecting the expression of any or all fragment of SEQ ID NO: 1 if only as small as 5 amino acid or 20 amino acid residues of SEQ ID NO: 1 is transfected and expressed on any or all cell lines from any or all animal origins.

22. 6) Nature of the invention. The nature of invention involves uninitiated experiments to mutate the 538 amino acids long polypeptide in many ways and detect the fusogenic activity afterward in any or all kinds of ell types as listed in claim 9.

23. 7) Lever of the skill in the art. The level of the skill in mutagenesis and reconstruction and expression a plasmid into ay or all kind of cell types is very high. However, as noted by

some of retrovirus study that there is a high unpredictable remain to be overcome in order for the skilled artisan to practice the full scope of the invention.

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

***Claim Rejections - 35 USC § 102***

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

25. Claims 1-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Jacobs et al. (US Patent No. 6,312,921B1).

26. Jacobs et al. disclose a gene AJ172-2 (SEQ ID NO: 4), which encodes a protein (SEQ ID NO: 4) with exactly same size and 100% identity to the claimed polypeptide. They teach to use northern blot and southern blot to detect its expression in variety tissue or cells from human and Monkey (Example 1 on col. 54-58, Fig. 2-3). They also teach that the AL172-2 like many previously described viral envelope proteins, can mediate cell-to-cell fusion events leading to the formation of giant synsytia. They demonstrate that transfections of full-length cDNA of AJ172-2 into cell lines including human or primate placenta cells, COS cells (monkey kidney SV40

transformed tumor cells), human Hela cells (Breast cancel cell) induce the formation of giant multiple nucleated syncytia by a fusogenic mechanism (col. 53-58, Fig. 4-7). Regarding to the vector limitation recited in claim 11, while Jacobs et al. is science about the cDNA of AJ172-2 that is carried by a vector, any transfection, it is well known in the art that transfection of a cDNA into a cell line and get it expressed, the cDNA must constructed in a plasmid vector that comprise a promoter that drive the inserted interest gene expression. Because the AJ172-2 is expressed in the transfected ell line, the CDNA is inherently carried by a plasmid containing a promoter. Therefore, the claimed invention is anticipated by the cited reference.

***Claim Rejections - 35 USC § 102***

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

28. Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Blond et al. (J. Virol. Feb. 1999, Vol. 73, No. 2, pp. 1175-1185).

29. Blond et al. teach that they isolate a human endogenous retrovirus-W (HERV-W), which encodes a protein (Fig. 7 on page 1183) with exactly same size and 100% identity to the claimed polypeptide. They teach to use northern blot and southern blot to detect its expression in variety human tissues (Fig. 1 on page 1177). Regarding to the fusogenic characristic, because the polypeptide disclosed by Blond has 100% identity to the claimed polypeptide, it inherently has the same functional characteristic even if the prior art. Therefore, the claimed invention is anticipated by the cited reference.

***Claim Rejections - 35 USC § 102***

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

31. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Alliel et al. (C.R. Acad. Sci III, August 1998, Vol. 321, no. 10, pp. 857-863).

32. Alliel et al. teach that they isolate a human endogenous retrovirus-W (HERV-W), which encodes a protein having a same size of 538 amino acid residues and 100% identity to the claimed polypeptide. They disclose that the expression of such protein in human tissues can be detected by northern blot and southern blot (See Fig. 3 on page 861). Regarding to the fusogenic catachrestic, because the polypeptide disclosed by the cited prior art has 100% identity to the claimed polypeptide, it inherently has the same biological function. Therefore, the claimed invention is anticipated by the cited reference.

33. For the above inherency rejection, Applicants' attention is directed to the MPEP 2051, which recites: ONCE A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIF-FERENCE "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product (See sequence search comparison attached).

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li
Art Unit 1648
April 21, 2004

James C. Housel 5/3/04

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

| Notice to Comply | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10,069,883 | | |
| | Examiner | Art Unit | |
| | BAOQUN LI | 1648 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Please comply the sequence rule according to the objection by office action

### Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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